

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/52, 9/00 // (A61K 31/52, 31:465)		A1	(11) International Publication Number: WO 96/00069
			(43) International Publication Date: 4 January 1996 (04.01.96)
(21) International Application Number: PCT/US95/07380		(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(22) International Filing Date: 9 June 1995 (09.06.95)			
(30) Priority Data: 08/264,666 23 June 1994 (23.06.94) US			
(71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).		Published <i>With international search report.</i>	
(72) Inventor: MAJETI, Satyanarayana; 7477 Greenfarms Drive, Cincinnati, OH 45224 (US).			
(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).			
(54) Title: TREATMENT OF NICOTINE CRAVING AND/OR SMOKING WITHDRAWAL SYMPTOMS WITH A SOLID OR SEMI-SOLID COMPOSITION CONTAINING NICOTINE AND CAFFEINE OR XANTHINE, ESPECIALLY FOR NASAL ADMINISTRATION			
(57) Abstract The subject invention encompasses a solid or semi-solid composition for the treatment or nicotine craving or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Treatment of nicotine craving and/or smoking withdrawal symptoms with a solid or semi-solid composition containing nicotine and caffeine or xanthine, especially for nasal administration.

BACKGROUND OF THE INVENTION

5 The health hazards from smoking tobacco are well known. Of the many by-products of combustion found in cigarette smoke, the substances most studied have been tars, carbon monoxide, and nicotine. Tars are the agents linked to the causation of various cancers and pulmonary diseases such as emphysema and chronic bronchitis. Carbon monoxide is a deadly gas which reduces the ability of blood
10 hemoglobin to carry sufficient oxygen. Carbon monoxide has also been causally linked to coronary artery disease and atherosclerosis. Nicotine appears to be the most pharmacologically active substance in tobacco smoke, yet it seems not to be as significant from a health standpoint as the tars and carbon monoxide. However, nicotine is the reinforcing substance in tobacco which maintains the addiction.

15 Various efforts have been made by smokers to discontinue smoking. Chewing beeswax, eating candy and peppermints as well as cold turkey interruption have been tried without much success. The addition of chemicals designed to sicken the user or otherwise render smoking repulsive to the user have also not produced good results. More recent therapies for smoking cessation have focused on the
20 administration of nicotine to the smoker. These therapies allow the individual to satisfy a nicotine habit while minimizing or eliminating side effects caused by absorbing nicotine through the lungs along with the other harmful by-products of combustion of tobacco.

 Nicotine supplementation has proven to be an effective therapy as an adjunct
25 to smoking cessation in helping to reduce the craving for smoking and provide relief from smoking withdrawal symptoms. However, there are many smokers for whom nicotine supplementation alone is inadequate. In accordance with the present invention, it has been discovered that a composition can be formulated which provides the combination of nicotine and caffeine or caffeine equivalent in a single
30 therapy. It has also been discovered that such a combination may offer the advantage of providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a broader spectrum of smokers who wish to break the smoking habit. It has further been discovered that these compositions may also curb the appetite which may aid in reducing the weight gain that is commonly experienced by
35 individuals who stop smoking.

 It is an object of the present invention to provide a composition comprising the combination of nicotine and caffeine or caffeine equivalent in a single therapy. It

is also an object of the present invention to deliver the nicotine and caffeine combination therapy in a convenient delivery system. It is a further object of the invention to provide a method for the treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms in individuals who wish to break or decrease the habit of smoking tobacco or the use of any tobacco product. These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to solid or semi-solid composition for the treatment of nicotine craving and/or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent, wherein the composition delivers from about 0.01mg to about 3mg of nicotine, and from about 1mg to about 30mg of caffeine or caffeine equivalent.

The present invention also relates to a method for providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a human or lower animal in need of such treatment comprising the administration of a safe and effective amount of a solid or semi-solid composition comprising nicotine and caffeine or caffeine equivalent.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention comprises nicotine, caffeine or caffeine equivalent, and preferably one or more pharmaceutically-acceptable carriers suitable for direct or indirect nasal administration. These compositions are useful for the treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms.

The terms "nicotine craving" and "smoking withdrawal symptoms" as used herein both refer to any physical or psychological reaction relating to breaking the habit of smoking tobacco or using any tobacco product or decreasing the frequency or intensity of smoking tobacco or using any tobacco product.

In general, the descriptive term "pharmaceutically-acceptable" is used herein to describe materials that are non-toxic and suitable for administration to humans and/or lower animals. The term "pharmaceutically-acceptable aqueous carrier" as used herein means any material safe and effective for use in the compositions of the present invention. Such materials include water, emollients, pH adjusters, emulsifiers, buffering agents, gel-forming compounds, aromatic compounds, solvents, preservatives, agents for regulating isotonicity, wetting agents, thickening agents, humectants, surfactants, agents for aiding the film-forming properties and substantivity of the formulations, antimicrobials for maintaining the antimicrobial integrity of the compositions, antioxidants, agents suitable for aesthetic purposes

such as fragrances, pigments, and colorings, non-soluble ingredients, and mixtures thereof.

5 The terms "safe and effective amount", as used herein, mean a sufficient amount of material to provide the desired benefit without undue adverse side effects commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific safe and effective amount will vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), and the specific formulation and optional components hereinafter.

10 The terms "suitable for direct or indirect nasal administration" as used herein refer to any formulation that is suitable for the convenient administration of the composition whereby the composition is placed in contact with mucous membranes of the nose, inhaled, or delivered in such a way that vapors of the composition are inhaled.

15 The following terms will be designated as follows: milligram as "mg", milliliter as "ml", nanogram as "ng", and microgram as "ug".

A detailed description of essential and optional components of the present invention is given below.

Nicotine

20 The present invention comprises nicotine. Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, which is freely water soluble, strongly alkaline, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic odor and turns brown on exposure to air or light [Physicians Desk Reference, 48th Edition, p. 1306, 1984]. Nicotine is
25 delivered in an amount of from about 0.01mg to about 3mg, preferably from about 0.1mg to about 2mg, and most preferably from about 0.5mg to about 1.5mg. Nicotine is also described in Remington's Pharmaceutical Sciences, 18th Edition, 1990, p. 891, which is incorporated herein by reference.

Caffeine

30 The present inventions also comprise caffeine or a caffeine equivalent. Caffeine is found as white, fleecy masses or long, flexible, silky crystals. It is odorless, bitter tasting, and slightly soluble in water and alcohol. Caffeine may be derived synthetically or by extraction of coffee beans, tea leaves or kola nuts [Hawleys Condensed Chemical Dictionary, Twelfth Edition, 1993]. Examples of
35 suitable sources of caffeine for use in the present invention are pure caffeine, caffeine combined with acetate, citrate, benzoate, phosphate, sulfate or salicylate. Also suitable are any of the xanthine analogues that match caffeine's effectiveness as a

central nervous system stimulant, including salts thereof that are compatible. Xanthine derivatives are described in Remington's Pharmaceutical Sciences, 18th Edition, 1990, pp. 1132-34, which is incorporated herein by reference. The caffeine or caffeine equivalent is delivered in an amount of from about 1mg to about 30mg, preferably from about 3mg to about 20mg, and most preferably from about 5mg to about 10mg.

Pharmaceutically-Acceptable Carrier

The invention compositions preferably also contain one or more pharmaceutically-acceptable carriers suitable for direct or indirect nasal administration. Such compositions include (but are not limited to) gels or jellies, emulsions, creams, ointments or other solid or semi-solid formulations suitable for directly or indirectly administering the present compositions intranasally. Preferred compositions are ointments, emulsions, gels and suspensions.

While the choice of nasal carrier is not critical to the present invention, the carrier or carriers chosen must be suitable for administering the nicotine and caffeine or caffeine equivalent so that the desired blood levels of these compounds are achieved in the body of the recipient. The desired blood level of nicotine is from about 1ng/ml to about 100ng/ml, preferably from about 5ng/ml to about 75ng/ml, and most preferably from about 10ng/ml to about 50ng/ml, preferably within 1 to 4 hours of administration. The desired blood level of caffeine or caffeine equivalent is from about 0.01ug/ml to about 20ug/ml, preferably from about 0.1ug/ml to about 15 ug/ml, and most preferably from about 0.5ug/ml to about 10ug/ml, preferably within 1 to 4 hours of administration.

The present compositions will normally be prepared in dosage unit form to contain safe and effective amounts of the nicotine and caffeine (or equivalent) to achieve the desired blood levels. Fractions of the dosage units or multiple dosage units may also be utilized. In general, the solid or semi-solid compositions herein deliver to a human or lower animal from about 0.01mg to about 3mg, preferably from about 0.1mg to about 2mg, and most preferably from about 0.5mg to about 1.5mg of nicotine; and from about 1mg to about 30mg, preferably from about 3mg to about 20mg, and most preferably from about 5mg to about 10mg, of caffeine or caffeine equivalent. Preferably the present invention may be a solid or semi-solid composition for the treatment of nicotine craving and/or smoking-withdrawal symptoms comprising nicotine, caffeine or caffeine equivalent, and one or more pharmaceutically-acceptable carriers suitable for indirect or direct nasal administration, wherein the composition delivers from about 0.01mg to about 3mg of nicotine, and from about 1mg to about 30mg of caffeine or caffeine equivalent.

The amount of nicotine and caffeine or caffeine equivalent and frequency of administration may vary depending on the carrier chosen and the personal needs of the user. However, it is suggested (as an example) that the present invention be administered from about once to about 20 times per day, preferably from about 2 to about 10 times per day, and most preferably from about 4 to about 8 times per day.

The compositions of the present invention may be prepared as emulsions. Single emulsion preparations, such as lotions and creams, of the oil-in-water type and water-in-oil type are well-known in the art and are useful in the present invention. Also useful in the present invention are multiphase emulsion compositions, such as the water-in-oil-water type, (as disclosed in U.S. Patent No. 4,254,105, Fakuda et al., issued March 3, 1981), and the triple emulsion systems comprising an oil-in-water-in-silicone fluid emulsion (as disclosed in U.S. Patent Application Serial No. 022,876, Figueroa, et al., filed March 6, 1987), both references incorporated herein. In general, such single or multiphase emulsions contain water, emollients and emulsifiers. Emulsions are described in detail in Remington's Pharmaceutical Sciences, 17th Edition, pp. 298-308, which is incorporated herein by reference.

Emulsion preparations useful in the present invention may also be prepared as ointments comprising a simple base of animal or vegetable oils or semi-solid hydrocarbons (oleaginous). Ointments may also comprise absorption ointment bases which absorb water to form emulsions. Examples of such ointment bases include anhydrous lanolin and hydrophilic petrolatum. Emulsion ointments may be oil-in-water or water-in-oil emulsions. Ointment carriers may also be water soluble. Examples of such ointment carriers include glycol ethers, propylene glycols, polyoxyl stearates, and polysorbates. A more detailed disclosure of suitable components for ointment bases can be found in Remington's Pharmaceutical Sciences, 17th Edition, pp.1573-1580

Water may also be present in the compositions. Water employed should preferably be deionized and free from organic impurities. Water may comprise from about 0% to about 50%, and preferably from about 20% to about 40%, by weight of the compositions. These amounts of water include free water which is added plus that which is introduced with other materials such as with sorbitol.

The composition may also comprise from about 1% to about 10%, preferably from about 2% to about 5%, of one or more pharmaceutically-acceptable emulsifiers. These emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, U.S. Patent 3,755,560, issued August 28, 1973, Dicert et al.; U.S. Patent 4,421,769, issued December 20, 1983, Dixon et al.; and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324

(1986); the disclosures of which are incorporated herein by reference. Preferred emulsifiers are anionic or nonionic, although the other types may also be used.

The composition may also comprise from about 2% to about 10% of a pharmaceutically-acceptable emollient and/or from about 0.1% to about 2% of a pharmaceutically-acceptable thickening agent which aids in adjusting the viscosity of the compositions. Suitable emollients include volatile silicone oils, non-volatile emollients such as fatty acid and fatty alcohol esters, highly branched hydrocarbons known as the Permethyl 99 through 108A series (available from Permethyl Corporation), and mixtures thereof. Suitable emollients are disclosed in U.S. Patent No. 5322689, to Hughes et al., issued 6/21/94, incorporated herein by reference.

Examples of suitable thickening agents include: cellulose derivatives (e.g., methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, and hydroxypropylmethyl cellulose), synthetic high molecular weight polymers (e.g., carboxyvinyl polymer and polyvinyl alcohol), plant hydrocolloids (e.g., karaya gum, xanthan gum, and tragacanth gum), clay thickeners (e.g., colloidal magnesium aluminum silicate and bentonite), and carboxyvinyl polymers are described in detail in U.S. Patent 2,798,053, Brown, issued July 2, 1975, incorporated herein by reference). A more complete disclosure of thickening agent useful herein can be found in Segarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 72-73 (1972), incorporated herein by reference.

The present compositions may also be prepared as gels. Such gels may be suspensions, or solutions. The gels may be hydrogels (with a water based solvent) or organogels (with a nonaqueous solvent). Xerogels, such as dry gelatin, tragacanth ribbons and acacia tears, and dry cellulose and polystyrene, are also useful in the present inventions. Pharmaceutically-acceptable gels may be prepared from gel forming compounds including but not limited to: natural gums such as guar gum; tragacanth; alginates and salts thereof; gelatin; carrageenan; cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, methylhydroxyethyl cellulose, ethyl cellulose, hydroxyethyl cellulose; carbomer; polyvinyl alcohol; polyoxyethylene-polyoxypropylene; pectin; xanthan gum; and mixtures thereof.

The present inventions may contain a pharmaceutically-acceptable surfactant. Typical surfactants useful in the present compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate, Polyoxyethylene 50 Stearate and Octoxynol, as well as Oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as tyloxapol). The usual concentration is from about 0.5% to 10%, by weight of the composition.

The compositions of the present invention may also include one or more pharmaceutically-acceptable solvents. The terms "pharmaceutically-acceptable solvent" refer to a solvent which possesses acceptable safety. The most typical example of such a solvent is water. Examples of other suitable organic solvents include: glycerin, propylene glycol, polyethylene glycol (200-600), polypropylene glycol (425-2025), glycerol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, butanediol, and mixtures thereof.

One or more pharmaceutically-acceptable humectants may also be included in the present compositions. A variety of humectants can be employed and may be present at a level of from about 1% to about 10%, more preferably from about 2% to about 8% and most preferably from about 3% to about 5%. These materials include urea; guanidine; glycolic acid and glycolate salts (e.g. ammonium and quaternary alkyl ammonium); triethanolamine; glycerol, lactic acid and lactate salts (e.g. ammonium and quaternary alkyl ammonium); polyhydroxy alcohols such as sorbitol, glycerin, hexanetriol, propylene glycol, hexylene glycol and the like; polyethylene glycol; sugars and starches; sugar and starch derivatives (e.g. alkoxylated glucose); D-panthenol; hyaluronic acid; lactamide monoethanolamine; acetamide monoethanolamine; and mixtures thereof. Preferred humectants are the C₃-C₆ diols and triols. Especially preferred is the triol, glycerin.

Most preferably, the compositions are isotonic, i.e., they have the same osmotic pressure as blood and lacrimal fluid. If desired, sustained release compositions, e.g., sustained release gels, can be conveniently employed. The desired isotonicity of the compositions of this invention may be accomplished by using, for example, sodium chloride or other pharmaceutically-acceptable agents such as dextrose, boric acid, sodium tartrate, sodium phosphate, potassium phosphate, propylene glycol or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

The compositions of the present invention also include microencapsulation of either the nicotine or caffeine (or caffeine equivalent) or both. Techniques and materials for microencapsulation are well known in the art. Microencapsulation is discussed more fully in Kirk and Othmer's Encyclopedia of Chemical Technology, Vol. 13, 2nd Edition, pp.436-456, which is incorporated herein by reference.

The compositions of the present invention may also contain one or more aromatic components. These aromatics include, for example, menthol, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); 2-dodecenal (citrus, mandarin); thymol;

cedar leaf oil, myristica oil, lavender oil, nutmeg oil, turpentine; 3-l-menthoxy propane-1,2-diol; N-substituted-p-menthane-3-carbox-amides and acyclic carboxamides; and mixtures thereof. Preferred are menthol, eucalyptol, thymol, cedar leaf oil, myristica oil, lavender oil, nutmeg oil, turpentine, and mixtures thereof.

- 5 Aromatic compounds may be present at a level of from about 0.0001% to about 1%, preferably from about 0.001% to about 1%, and most preferably from about 0.001% to about 0.5%, by weight of the compositions.

Other pharmaceutically-acceptable ingredients may also be present including but not limited to: pH adjusters such as sodium hydroxide; buffering agents such as
10 sodium bicarbonate; preservatives such as benzyl alcohol, parabens, benzalkonium chloride, chlorhexidine gluconate and disodium EDTA; surfactants, plasticizers; wetting agents; various polymers for aiding the film-forming properties and substantivity of the formulations; antimicrobials for maintaining the antimicrobial integrity of the compositions; antioxidants; agents suitable for aesthetic purposes
15 such as fragrances, pigments, and colorings; and mixtures thereof.

The compositions may also contain low levels of pharmaceutically-acceptable insoluble ingredients added, for example, for visual effect purposes, e.g., thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl)
20 phenyl 4-alkyl(oxy)benzoates available from Hallcrest, Glenview, Illinois 60025, U.S.A.

Method of Treatment

The present invention also encompasses a method of treatment. The method of providing treatment and/or relief of nicotine craving and/or smoking withdrawal
25 symptoms to a human or lower animal in need of such treatment, as, disclosed herein, comprises the administration of a safe and effective amount of a solid or semi-solid composition comprising nicotine and caffeine or caffeine equivalent. Such compositions preferably further comprise one or more pharmaceutically acceptable carriers suitable for direct or indirect nasal administration.

30 The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

35

EXAMPLE I

Ointment Base Composition

An ointment base composition according to the present invention is prepared as follows:

	<u>Ingredient</u>	<u>Weight %</u>
	Petrolatum (White)	40.0
5	L-Menthol	2.8
	Lavender Oil	4.3
	Bornyl Acetate	5.2
	Triethanolamine	0.5
	Acrylates/Steareth-20 Methacrylate	0.3
10	Copolymer	
	Disodium EDTA	0.1
	Caffeine	10.0
	Nicotine	1.0
	Water	35.8

15

¹ Available as Acrosyl ICS-1 from Rohm and Haas

Petrolatum is added to a suitable size container and heated to about 50°C. While mixing at a moderate speed, the, L-menthol, lavender oil and bornyl acetate are added and mixed until uniform. In a separate vessel, some of the water and triethanolamine are combined. In a separate vessel, the disodium EDTA is added to a portion of the water, mixed until completely dispersed, then heated to about 70°C. The oil phase (petrolatum mixture) is added to the water phase with mixing (high shear, for example, a Tek Mar mixer). Cool the resulting mixture to about 40°C and add the triethanolamine solution. The resulting combination is then cooled to room temperature.

25

What is Claimed is:

1. A solid or semi-solid composition for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent, wherein the composition delivers:
 - a) from 0.01mg to 3mg of nicotine; and
 - b) from 1mg to 30mg of caffeine or caffeine equivalent.
2. The composition according to Claim 1 wherein (b) is caffeine.
3. A solid or semi-solid composition for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine, caffeine or caffeine equivalent, and one or more pharmaceutically-acceptable carriers suitable for direct or indirect nasal administration, wherein the composition delivers:
 - a) from 0.01mg to 3mg of nicotine; and
 - b) from 1mg to 30mg of caffeine or caffeine equivalent.
4. The composition according to Claim 3 wherein the composition is in the form of an ointment based emulsion.
5. The composition according to Claim 4 wherein (b) is caffeine.
6. The composition according to Claim 4 wherein (b) is the caffeine equivalent xanthine.
7. The solid or semi-solid composition according to Claim 3 comprising:
 - a) from 0.1mg to 2mg of nicotine;
 - b) from 3mg to 20mg of caffeine or caffeine equivalent.
8. The composition according to Claim 7 wherein the composition further comprising one or more aromatic compounds selected from the group consisting of menthol, eucalyptol, thymol, cedar leaf oil, myristica oil, lavender oil, nutmeg oil, turpentine, and mixtures thereof.
9. The composition according to Claim 8 further comprising from 0.01% to 5% of a pharmaceutically-acceptable humectant.

10. The composition according to Claim 9 further comprising from 0.5% to 10% of a pharmaceutically-acceptable surfactant.
11. The composition according to Claim 10 wherein the composition is in the form of a nasal gel.
12. The composition according to Claim 10 wherein the composition is in the form of a solid wherein vapors from the solid are inhaled.
13. The composition according to Claim 10 wherein the composition is in the form of an ointment wherein the nasal cavity is coated with the ointment.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 95/07380

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/52 A61K9/00 //(A61K31/52,31:465)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 778 677 (G.K. EBBESEN) 18 October 1988 see the whole document ---	1-13
Y	TOXICOL APPL PHARMACOL (UNITED STATES), JUN 30 1985, VOL. 79, NO. 2, PAGE(S) 268-73, Tariq M et al 'Effect of nicotine and caffeine pretreatment on the gastric mucosal damage induced by aspirin, phenylbutazone, and reserpine in rats.' see the whole document --- -/--	1-13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- '&' document member of the same patent family

Date of the actual completion of the international search

4 October 1995

Date of mailing of the international search report

13.10.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Stierman, B

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 95/07380

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. OF NEUROCHEMISTRY, vol.61, no.5, 1993 pages 1901 - 1906 Wilson S P 'Pertussis toxin enhances proenkephalin synthesis in bovine chromaffin cells' see the whole document ---	1-13
Y	DE,A,35 06 406 (STROMBERG H.-J.) 28 August 1986 see the whole document ---	1-13
Y	PHARMACOL BIOCHEM BEHAV (UNITED STATES), APR 1994, VOL. 47, NO. 4, PAGE(S) 919-36, Cohen C et al 'Caffeine antagonizes EEG effects of tobacco withdrawal.' see the whole document ---	1-13
Y	US,A,5 051 426 (F.W. PARNELL) 24 September 1991 see the whole document ---	1-13
Y	US,A,4 568 676 (J.B. SMITH) 4 February 1986 see the whole document ---	1-13
Y	PSYCHOPHARMACOLOGY (BERL) (GERMANY), JAN 1994, VOL. 113, NO. 3-4, PAGE(S) 438-44, Perkins KA et al 'Subjective and cardiovascular responses to nicotine combined with caffeine during rest and casual activity.' see the whole document ---	1-13
Y	J ETHNOPHARMACOL (SWITZERLAND), MAR 1985, VOL. 13, NO. 1, PAGE(S) 3-49, 'A multidisciplinary overview of intoxicating snuff rituals in the western hemisphere.' see page 30 - page 31 see page 35 - page 36 ---	1-13
Y	US,A,4 959 380 (J.E. WILSON) 25 September 1990 see the whole document ---	1-13
Y	US,A,5 288 497 (T.H. STANLEY ET AL.) 22 February 1994 see the whole document see claims 163,199,219 ---	1-13
-/--		

INTERNATIONAL SEARCH REPORT

Int. Patent Application No
PCT/US 95/07380

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BUNDESVERBAND DER PHARM. INDUSTRIE E.V. 'Rote Liste 1987', EDITIO CANTOR, AULENDORF/WÜRTT., DEUTSCHLAND see no. 71093: "Chinorhin" and no. 71095: "Emser Nasensalbe echt" ---	1-13
A	ADDICT BEHAV (ENGLAND), MAY-JUN 1994, VOL. 19, NO. 3, PAGE(S) 229-56, Swanson JA et al 'Caffeine and nicotine: a review of their joint use and possible interactive effects in tobacco withdrawal.' see the whole document -----	1-13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/07380

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4, 7-13
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Expressions like "a solid or semi-solid composition", caffeine equivalent" etc. do not make sufficiently clear, which compound/compositions are meant. The search has therefore been restricted to the compounds and compositions explicitly mentioned in the claims and to the general inventive concept.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int. Patent Application No

PCT/US 95/07380

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4778677	18-10-88	NONE	
DE-A-3506406	28-08-86	EP-A, B 0192950	03-09-86
US-A-5051426	24-09-91	US-A- 5219858	15-06-93
US-A-4568676	04-02-86	NONE	
US-A-4959380	25-09-90	NONE	
US-A-5288497	22-02-94	US-A- 4671953	09-06-87
		AU-B- 5521894	28-04-94
		AU-B- 645265	13-01-94
		AU-B- 6287790	08-04-91
		EP-A- 0490916	24-06-92
		EP-A- 0630647	28-12-94
		JP-T- 5503917	24-06-93
		WO-A- 9103237	21-03-91
		US-A- 5132114	21-07-92
		US-A- 5288498	22-02-94
		AT-T- 116131	15-01-95
		CA-A- 1271421	10-07-90
		DE-D- 3650189	09-02-95
		DE-T- 3650189	04-05-95
		EP-A, B 0200490	05-11-86
		EP-A- 0487520	03-06-92
		EP-A- 0490891	24-06-92
		EP-A- 0404205	27-12-90
		US-A- 4863737	05-09-89
		US-A- 4885173	05-12-89
		WO-A- 9103099	07-03-91
		WO-A- 9103234	21-03-91
		US-A- 5122127	16-06-92